The Historic FDA and NIDA Meetings on "Hallucinogens"

by Rick Doblin, MAPS President

FOR the first time in fourteen years, on July 13 and 14, 1992 in Bethesda, Maryland, the National Institute on Drug Abuse (NIDA) convened a Technical Review meeting on "hallucinogens". In an impressive display of interagency synchronization, NIDA's Technical Review immediately preceded the July 15 meeting of the FDA's Drug Abuse Advisory Committee. The FDA committee reviewed general policies regarding "hallucinogenic" research and specific issues concerning the MDMA research protocol of Dr. Charles Grob which MAPS helped to develop.

The consensus of the experts at these two meetings was that there were significant scientific benefits to be gained by administering psychedelics to human subjects in order to research the brain's basic physiological mechanisms and their psychological correlates. Most importantly, the experts thought that these scientific benefits outweighed the estimated risks to subjects and society from conducting the research. The FDA's Drug Abuse Advisory Committee recommended that psychedelic research protocols be required to meet the rigorous scientific standards that the FDA applies to studies involving any other drugs.

As a result of the NIDA and FDA meetings, human research with MDMA and the classic psychedelics is now possible. What follows is a report on these two crucial meetings.

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"Hallucinogens: An Update" — The NIDA Technical Review

NIDA organizes Technical Review meetings on a wide variety of subjects. At these meetings NIDA convenes some of the nation's leading experts on a particular topic to discuss the latest findings from their research. Some of the presenting researchers usually have been funded by NIDA while others will have found funding from sources such as foundations, pharmaceutical companies, and universities. Officials with other governmental agencies and interested members of the public may also attend. The meetings are tape recorded and the scientific papers on which the talks are based are gathered together and published in NIDA's Technical Review series.

Fourteen years had elapsed since NIDA had last scheduled a Technical Review on "hallucinogens." This lengthy hiatus was largely due to the paucity of scientific advances, since human studies had been essentially prohibited by the government. There were, however, several important reasons for NIDA to have convened a Technical Review at this time. Unlike human studies, animal studies had been permitted all along and had yielded some tantalizing clues about the basic functioning of the brain, in particular of the serotonin neurotransmitter system. Furthermore, out of a frustration with the success rates of traditional drug treatment methods, NIDA's Medications Development Division was beginning to investigate the possible use of psychedelics, specifically the African root ibogaine, in the treatment of drug addiction. NIDA was also concerned about the use of psychedelics outside legal contexts which had not disappeared under ever tougher drug laws but is reported instead to be on the increase, according to NIDA's Household Survey data and DEA reports.

On July 13 and 14,1992, NIDA gathered together almost twenty scientists for a two-day meeting. Among these were three researchers familiar to many MAPS members: Rick Strassman, a psychiatrist at the University of New Mexico who has reported on his basic research with DMT in several MAPS newsletters, Sasha Shulgin, an independent researcher whose book PIHKAL (co-authored with his wife Ann) was reviewed in the last newsletter, and David Nichols, a medicinal chemist at Purdue University who manufactured the MDMA that was used in the pre-clinical animal studies used by MAPS to open its FDA Drug Master File on MDMA at the FDA.Rick Strassman and Dave Nichols have both received government funding for portions of their research.

The opening speaker was Stephen Szara, the retired chief of NIDA's Biomedical Research Branch. He outlined the history of psychedelic research and identified six distinct eras. The first, from the early 1900's to the late 1940's, was the Hallucinogen Era in which these drugs were considered to produce distortions of normal consciousness that provided users with a glimpse into the experiential world of the insane. The Psychotherapeutic Era, which lasted

from the late 1940's to the early 1960's, developed in response to numerous reports that these drugs also produced experiences of profound insight, clarity, and deep emotionality that might have therapeutic potential. The Psychedelic Era, in the early to mid 1960's, involved the increasing use by researchers of large doses of psychedelics with the aim of producing powerful, transcendent, cathartic experiences in a wide range of subjects such as ministers, prisoners, alcoholics, and terminal cancer patients. The Psychedelic Era, as we are all aware, also included an explosion of the non-medical use of psychedelics by young people in a counter-cultural movement linked to anti-war protests. The Behavioristic Era, in the late 1960's to the early 1970's, involved the use of psychedelics in animals by researchers seeking to understand the basic relationship between brain chemistry and behavior. The Era of Legal Limbo, from the early 1970's to the present, involved the cessation of human studies though some animal research continued.

According to Dr. Szara, the beginning of a new era, which he calls Psychoheuristic, is underway. He coined the word "psychoheuristic" to indicate that these drugs can be used as research tools to understand the workings of the human psyche. He intended the word "psychoheuristic" to focus attention on the context created by the people who administer the drug rather than on the drug itself, highlighting the fundamental lesson learned from previous studies about the importance of the set and setting in shaping the incredible variety of experiences psychedelics can catalyze. Dr. Szara noted that from 1953 to 1973 the US government funded at least 116 studies of LSD with over 1700 subjects at a cost of about $4 million dollars. He concluded that careful research into the mysterious workings of the brain with uniquely useful psychedelic tools could yield new discoveries of significant potential.

Most of the remaining presentations focused on the use of psychedelics in animal studies, both to understand the functioning of the serotonin system and to develop methods of testing new compounds for psychoactivity. These presentations became highly technical and mostly went over my head. I was particularly impressed by the incredible ability scientists have to map the structure and function of molecules, of brain neurotransmitter sites, and even of the sections of the DNA itself responsible for the manufacture of various brain cells and the chemical compounds found therein. What I was able to understand was that psychedelic drugs are providing scientists with the tools needed to probe the serotonin system with an extraordinary degree of specificity.

Rick Strassman focused on findings from his work with DMT in eleven human volunteers. He reported that it took him about two years of effort to receive final FDA approval to evaluate DMT's physiological effects and develop a questionnaire to measure the psychological effects of DMT and other hallucinogenic drugs. His groundbreaking research clearly demonstrated that human studies with psychedelics could be conducted safely and that valuable scientific data could be generated.

Sasha Shulgin's presentation reviewed the work he and his wife Ann have written about in PIHKAL in which he synthesized hundreds of novel psychoactive compounds and tested them for activity in himself and a team of twelve research associates. He emphasized the incredible subtlety and unpredictability of the relationship between the structure of a compound and its psychoactivity. He cited instances where data from animal studies was contradicted by data from human reports and made an impassioned plea for more human studies. He referred to Stephen Szara's reference to the use of psychedelics to produce experiences of a religious, mystical nature and asked the assembled researchers and government officials to tell him how they would ever get rats to provide sufficient data on those matters. The response was, of course, only laughter. One subsequent speaker, however, prefaced his talk on the effects of psychedelics in animals by acknowledging the courage of Sasha Shulgin and Rick Strassman in gathering human data, which he felt provided essential clues in interpreting the animal data.

At the conclusion of the meeting, Dr. Geraline Lin, the chairperson of the

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meeting, asked the group for a summary of their sense of the current state of research and of future directions to explore. The scientists felt confident that animal models were useful in helping to predict the psychoactive characteristics of novel compounds and in understanding the structural and functional aspects of the brain's serotonin neurotransmitter system. However, most scientists felt that animal studies had limited relevance unless correlated with human data and they were generally supportive of further studies in humans.

Rainbows over FDA

In the evening after the conclusion of the NIDA Technical Review meeting, with the FDA meeting scheduled to begin the next morning, Charles Grob and I had a lot to think about. Though it was raining on and off, we decided to take a walk from our hotel to the FDA building to help focus our thoughts. As we approached the massive but deserted Parklawn building, where during the day thousands of federal government employees work, we were presented with an amazing sight. Rising over the building, in the watery haze left by a rain cloud, shone a complete rainbow. Though we value rationality as much as the next person, we were sorely tempted to consider it a favorable omen.

The FDA's Drug Abuse Advisory Committee Meeting

Since the Federal Advisory Committee Act of 1972, the FDA has used expert advisory committees to provide guidance and advice on important matters coming before it. Such matters include the final review of data concerning the approval of a drug for marketing (called a New Drug Application or NDA) and more rarely on the approval of a research protocol (called an Investigational New Drug application or IND) . The FDA has created about 17 different advisory committees, each composed of eleven members who serve for several years and meet about once or twice a year. The meetings are always tape recorded, often filmed, and transcripts are made of all comments. Though the FDA retains final authority to make decisions, the recommendations of the committee are almost always taken. The most widely publicized recent use of an FDA Advisory Committee concerned the review of the safety of breast implants.

In the last newsletter I reported that after almost two years of preparation, Charles Grob had submitted to the FDA's Pilot Drug Evaluation Staff (PDES) a protocol designed to investigate the use of MDMA in the treatment of pain and distress in end-stage cancer patients. I indicated that the PDES had four basic options; approve the protocol, reject it, place it on hold pending more pre-clinical animal studies or present it to an advisory committee. As it turned out, the PDES suggested several significant changes in the protocol design and choose to present the IND, along with their critique and our response, to its Drug Abuse Advisory Committee.

The PDES also gave the Advisory Committee the task of considering policies for "hallucinogenic" research in general. Within the last year, the PDES has approved several applications for psychedelic research with DMT and LSD and will soon be presented with applications to research ibogaine and psilocybin. Since there is renewed scientific interest in the field of psychedelic research, the PDES felt a need for the guidance and backing provided by the Advisory Committee. Procedurally, the Committee met in open session to discuss general policies toward psychedelic research. It then went into closed session for the discussion of the MDMA protocol, allowing in only other government officials from NIDA, DEA and the White House Office of Drug Control Policy (the Czar's office) and participants specifically invited by Charles Grob.

To aid the Committee in its deliberations, the PDES arranged for six expert witnesses to address the committee in open session. These included MDMA neurotoxicity experts Dr. Lewis Seiden (U. of Chicago) and Dr. George Ricaurte (Johns Hopkins), esteemed researchers Dr. Reese Jones (UCSF) and Dr. Murray Jarvik (UCLA), and Rick Strassman and

David Nichols, both of whom were also at the NIDA meeting. Charles Grob was given an opportunity to address the Committee during the closed session concerning details of the MDMA protocol design. From the opening moments of the meeting to the conclusions reached at the end, the participants were privileged to witness the triumph of science over ideology. The first person to address the Committee was, to my surprise, NIDA's Dr. Geraline Lin. She reported on the Technical Review meeting and indicated that the participants had reached consensus on the need to conduct human studies with "hallucinogens" for two basic purposes, to investigate their biological correlates and therapeutic utility. She stressed the need for well-controlled, objective human studies that would enable regulators to balance therapeutic uses with risks, toxic and otherwise. With NIDA unexpectedly weighing in on the side of research, the probability that the Committee would approve the protocol seemed to rise dramatically.

The real star of the meeting was, however, Reese Jones. He began cautiously by pointing out the problems involved in obtaining genuine informed consent from research subjects. He recommended that the therapists conducting the studies not conduct the initial subject screening because the delicate nature of any therapeutic relationship they might develop with the potential subject could give them undue influence. He pointed out the difficult issue of ensuring that training psychiatrists conducting psychedelic research be properly trained in the administration of psychedelics.

He then switched gears and reminded the Committee that psychedelic researchers are pioneers without the large resources of pharmaceutical companies behind them. He urged the Committee not to demand that they conduct the ideal protocols the first time out but rather let them begin by conducting more limited but nevertheless scientifically rigorous studies. He strongly criticized alarming interpretations of MDMA neurotoxicity data. He conjectured that since MDMA-related serotonin depletion in animals was seemingly without harmful behavioral and physiological correlates and human users reported beneficial effects from MDMA, serotonin depletion, if it even occurred, could as easily be considered advantageous as dangerous. He quipped that a pharmaceutical company with a drug that produced beneficial effects that people desired with possible permanent brain changes would prominently feature the brain changes in their advertisements and make them a major selling point.

Rick Strassman spoke briefly about his DMT work, summarizing the data that he reported more fully at the NIDA meeting. He primarily made the point that human studies could be safely conducted.

When George Ricaurte discussed some of his concerns about neurotoxicity, he was aggressively questioned by Reese Jones who opined that MDMA neurotoxicity reminded him of the LSD chromosome damage scare of the 1960's which helped generate fear of LSD and contributed to the cessation of LSD research but was later proved groundless. This interchange was rather dramatic, a snippet of which was broadcast around the world in CNN's television news story on the meeting.

Lewis Seiden spoke to the Committee about the cultural aspects of the history of psychedelic research, seeking to help them view the protocol more dispassionately. He also observed that some behavioral correlates of massive serotonin depletion have been found in some studies and that concern over MDMA's neurotoxic potential was not scientifically inappropriate.

The MDMA protocol discussion.

The meeting then went into closed session. It began with a presentation by Charles Grob. I have never seen him quite so nervous, perhaps because he went to medical school to be able to conduct psychedelic research and was finally faced with that possibility. His sincerity and his careful preparation were evident to the Committee. He had chosen to strongly

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We put the FDA to the test, and they passed. Now they are testing us.

rebut some of FDA's protocol critiques, a delicate task. In addition, he was asking to make a major change in the protocol and proposed separating the study into two parts, a neurotoxicity safety study in normals and an efficacy study in cancer patients. Though he was willing to conduct spinal taps on cancer patients if the FDA insisted (the oncologist working on the study had no objections to this), he much preferred not to. He argued that the neurotoxicity data would be better in any case if we eliminated the confounding effects of the patient's terminal illness and instead used healthy normals for that study.

During the ensuing discussion, Rick Strassman reported that he had divided his DMT subjects into two groups, those previously exposed to MDMA an average of ten times (MDMA Positives) and those exposed to MDMA an average of less than one time (MDMA Negatives). He compared the physiological reactions of both groups to DMT, which has powerful effects on the serotonin system. He found no significant differences between the MDMA Positives and the MDMA Negatives.

Dr. Curtis Wright, the FDA official directing the review of the protocol, asked George Ricaurte what he thought of the extent of the neurotoxic risk to the proposed subjects from MDMA. After considered reflection, George Ricaurte stated that the doses called for in the experiment would not pose a large risk to the subjects, either in the cancer patients or the normals. At this point, we knew for sure that the Committee would approve the study.

The Committee then discussed various aspects of the protocol and suggested several changes. Curtis Wright suggested that the Committee not get bogged down in details, which the FDA staff could better handle at a later time, but should consider two basic questions. First, should human studies with MDMA and other psychedelics be conducted? And if so, was psychedelic research sufficiently unique such that a new set of standards and procedures needed to be created to evaluate the studies?

As we held our breath, we listened to the Committee decide that the benefits of gathering scientific information about MDMA and other "hallucinogens" through the use of human studies warranted the risks to subjects and society of conducting such research. The Committee also felt that research into the medical uses of "hallucinogens" was most appropriately regulated in the same manner and held to the same rigorous scientific standards for safety and efficacy as medical research with any other drug that the FDA would be asked to review. Finally, the Committee suggested that the FDA assist Charles Grob in the design of two studies, a standard Phase 1 study to investigate the safety of MDMA in healthy subjects and a standard Phase 2 study to investigate the efficacy of MDMA in the treatment of pain and distress in end-stage pancreatic cancer patients. For almost two years, Charles Grob and I and numerous others have worked on this protocol as a labor of love, in hopes of bringing it to the point where research into MDMA's therapeutic potential could begin. Our success was made possible by many people's hard work, as far back as 1984 when the DEA first moved to make MDMA illegal and even before, when courageous people pioneered the therapeutic use of MDMA.

As a MAPS member you have been an essential part of this effort. With your financial support we can achieve a genuine breakthrough. Foundations and government agencies may support future studies, but will probably not be of assistance until we have some solid data in hand. There are no more governmental roadblocks on the path immediately ahead of us. We put the FDA to the test, and they passed. Now they are testing us. As the President of MAPS, I am asking you to contribute whatever you can in support of this research. ■